Acne Vulgaris: Developing Drugs for Treatment

September 19, 2005 – Docket No. 2005D-0340

Coria Laboratories – Comments

Clause No. / Section	Paragraph/Figure/ Table/Note	Comment (Justification for Change)	Proposed Change
II. A. – Clinical Background: Lesion Types	Lines 65-76	The definitions of lesion types are inappropriate: Closed comedones are NOT precursors to the larger inflammatory lesions; also the North American standard for the definition of a nodule is 1 cm as opposed to 5 mm.	Definitions should reflect those commonly recognized in medical references such as Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 5th Edition.
II. B. – Clinical Background: Overall Acne Severity	Lines 87-89	A scale for the Investigator's Global Assessment (IGA) should be established to allow consistency between various acne studies and between investigators in a multicenter study.	This scale should be developed jointly between professional associations, industry and the Agency to ensure all goals are achieved for providing an acceptable, consistent scale for the IGA evaluation.

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III. A. 1. – Drug Development Plan: Clinical Considerations – General	Lines 109-110	There is concern about utilizing a post-treatment follow-up period to evaluate the recurrence of acne following treatment discontinuation. In our opinion, it is unfair to the patient to require follow-up as it is well known that there is no cure for acne. A patient should not be denied treatment during that follow-up period if treatment is warranted. Retinoids do not maintain improvement after they are stopped. The disease should be allowed to run its course and medication should be used during disease flares. Use of a follow-up period will bias the outcome of the study depending on the class of treatment being used. A follow-up period in which drug is not provided during active disease is not the "real-world" use of medications such a tretinoin.	Remove this recommendation for treatment follow-up.
III. A. 3. – Drug Development Plan: Targeted Acne Therapy	Line 157	Assessments of "global severity" that ignore lesion counts are subjective, imprecise, and poorly standardizable. They offer no advantage and place a crude method of grading on the same plane as a well-standardized and validated method.	Remove the requirement that discusses the assessment of global severity that ignores lesion counts.
III. A. 3. – Drug Development Plan: Targeted Acne Therapy	Lines 159-166	'Appropriate non-inferiority margin' should be defined to allow consistency amongst acne studies.	Establish a pre-defined, non-inferiority margin for consistent assessment.

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III. A. 3. – Drug Development Plan: Targeted Acne Therapy	Lines 166-168	The draft guidance recommends that the applicant specify if a drug product would be indicated for only inflammatory, only non-inflammatory, or both types of lesions of acne before the initiation of Phase 3 studies. This may be difficult to predict at this stage of development. The result of this recommendation would be that many applicants would move ahead with only inflammatory lesions as these are the most easily treated. It is our opinion that the accuracy of prediction at Phase 2 is far less than most appreciate or have understanding of. The mechanism of action of the drug would need to be fully understood in order to accurately predict.	If the mechanism of action is fully understood, then the choice of lesion to be treated can be made on this basis. However if the mechanism of action is unknown, this recommendation should be removed.
III. A. 3. – Drug Development Plan: Targeted Acne Therapy	Lines 170-173	The expectation that if the drug product may be used together with another marketed drug therapy for acne, that the clinical study design reflects the co-use or adjuvant use is unreasonable. As mono-therapy treatment in acne is rare, it is unreasonable to expect the sponsor of a new drug to study the drug in every possible concomitant situation. Ideally, a study of this nature should not be required for drug approval, but would be more appropriate being performed as a post-approval study when one knows more about how the drug product is actually being prescribed by the treating physician.	Remove the expectation that if the drug product may be used together with another marketed drug therapy for acne, that the clinical study design reflect the co-use or adjuvant use.
III. A. 5. – Drug Development Plan: Safety Considerations	Lines 208-209	The basis for a waiver of phototoxicity and photosensitization studies does not provide the analytical conditions under which the absorption should be determined. This could be particularly important because of the absoluteness of '…no absorption…".	A threshold should be jointly established between Agency and Industry/Professional experts to ensure relevance or appropriateness of the phototoxicity/photosensitization waiver.

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IV. 1) – Study Design: Sample Size	Lines 275-277	'Non-inferiority margin' should be defined to allow consistency amongst acne studies.	Establish a pre-defined, non-inferiority margin for consistent assessment.
IV. A. 1. – Study Design: Primary Endpoints	Lines 355-357	The recommendation that each subject's improvement be verifiable (e.g., via photographs) by staff for auditing purposes is unreasonable. Currently, technology is not available to provide 'perfect' photographs for accurate subject assessment. In addition, this recommendation would create a financial burden on study sponsors, as a tremendous expense would be incurred to provide the appropriate technology to all study sites. In addition, it is unclear what is meant by the term 'auditing purposes'. Does this mean that the Agency will be checking acne grading for purposes of product approval, or is this a simple verification of subject participation? More explanation is needed of this term.	Remove the recommendation that each subject's improvement be verifiable for auditing purposes from this guidance.
IV. A. 2. – Study Design: Lesion Counts	Lines 395-397	It is unreasonable to request that nasal lesions be included in the count for facial acne lesions. The presence of trichostasis spinulosa confounds grading in many patients. Not counting nasal lesions has been an effective means of eliminating this problem.	Remove the requirement to include nasal lesion counts in the count for facial acne lesions.
IV. B. – Study Design: Patient Reported Outcomes	Lines 406-409	We are in agreement that patient reported outcome information is of interest. However, this information should be evaluated more closely with data being allowed in the approved product labeling.	The Sponsor, at their discretion, should be able to utilize information obtained from patient reported outcome data in the approved product labeling.
V. A. 1) c) – Data Analysis	Line 424	The dichotomous success rate is an artificial analysis required by the FDA. It provides very low success rates and tends to provide inconsequential outcomes.	Use the 7-point static scale upon which the dichotomous "success/fail" analysis is based; perform an analysis of the distribution across treatment groups.

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V. A. 2) – Data Analysis	Lines 434-440	The dichotomous success rate is an artificial analysis required by the FDA. It provides very low success rates and tends to provide inconsequential outcomes.	Global analysis should be demoted to a secondary analysis.
V. A. 2) – Data Analysis: Handling Dropouts	Line 511-516	In clinical trials which are intended to evaluate the safety and efficacy of products, it is desirable to encourage subjects to complete the course of therapy and complete the study. Dropouts may actually provide information regarding the safety and efficacy of treatment. Establishing the score that is appropriate and consistent with the reasons for drop out should be the goal of a sound scientific study. While it is important to demonstrate that studies are robust with the process for handling dropouts, it is our position that assigning the best possible score to all dropouts on placebo and the worse possible score to all dropouts on the active treatment has no scientific basis, especially if the reason for drop out is influenced by the lack of efficacy and/or an adverse event. The concept of giving the best score to a subject on placebo (by definition a subject receiving little or no therapeutic benefit) and the worst score to subjects on active treatment, may introduce a bias in the analysis that would be contrary to the purpose of the clinical trial and sound clinical research.	The sensitivity analysis should not be a mandatory analysis.